California Institute for Regenerative Medicine

Systematic identification of cis-regulatory sequences active in mouse and human embryonic stem cells.

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Authors: Marica Grskovic, Christina Chaivorapol, Alexandre Gaspar-Maia, Hao Li, Miguel Ramalho-Santos

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Public Summary:

Scientific Abstract:
Understanding the transcriptional regulation of pluripotent cells is of fundamental interest and will greatly inform efforts aimed at directing differentiation of embryonic stem (ES) cells or reprogramming somatic cells. We first analyzed the transcriptional profiles of mouse ES cells and primordial germ cells and identified genes upregulated in pluripotent cells both in vitro and in vivo. These genes are enriched for roles in transcription, chromatin remodeling, cell cycle, and DNA repair. We developed a novel computational algorithm, CompMoby, which combines analyses of sequences both aligned and non-aligned between different genomes with a probabilistic segmentation model to systematically predict short DNA motifs that regulate gene expression. CompMoby was used to identify conserved overrepresented motifs in genes upregulated in pluripotent cells. We show that the motifs are preferentially active in undifferentiated mouse ES and embryonic germ cells in a sequence-specific manner, and that they can act as enhancers in the context of an endogenous promoter. Importantly, the activity of the motifs is conserved in human ES cells. We further show that the transcription factor NF-Y specifically binds to one of the motifs, is differentially expressed during ES cell differentiation, and is required for ES cell proliferation. This study provides novel insights into the transcriptional regulatory networks of pluripotent cells. Our results suggest that this systematic approach can be broadly applied to understanding transcriptional networks in mammalian species.

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